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<b>(21) International Application Number:</b> PCT/US93/08156 <b>(22) International Filing Date:</b> 3 September 1993 (03.09.93) <b>(30) Priority data:</b> 07/958,053 6 October 1992 (06.10.92) US <b>(60) Parent Application or Grant</b> (63) Related by Continuation US 07/958,053 (CON) Filed on 6 October 1992 (06.10.92) <b>(71) Applicant (for all designated States except US):</b> THE UP-JOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).		<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> TOMICH, Paul, Kosta [US/US]; 3703 Blackberry Lane, Kalamazoo, MI 49008 (US). BOHANON, Michael, John [US/US]; 31640 28th Avenue, Gobles, MI 49055 (US). LAJINESS, Michael, S. [US/US]; 28293 Springbrook, Lawton, MI 49065 (US). FUJITA, Yoshiji [JP/JP]; Namiki-6-8-6-302, Abiko-shi, Chiba 270-11 (JP). TSUZUKI, Kazuo [JP/JP]; Yatabe 1054-19, Tsukuba-shi, Ibaraki 305 (JP).  <b>(74) Agent:</b> WELCH, Lawrence, T.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).  <b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> USE OF 4-HYDRAZONO-1,4-DIHYDRO-PYRIDINE AND/OR 4-HYDRAZINO-PYRIDINE DERIVATIVES FOR TREATMENT OF HYPERTENSION AND CONGESTIVE HEART FAILURE		
<b>(57) Abstract</b>  The present invention provides the use of certain known 4-hydrazono-1,4-dihydro-pyridine and 4-hydrazino pyridine compounds for the treatment of hypertension and congestive heart failure.		

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 93/08156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4980379	25-12-90	NONE	

USE OF 4-HYDRAZONO-1,4-DIHYDRO-PYRIDINE AND/OR  
4-HYDRAZINO-PYRIDINE DERIVATIVES FOR TREATMENT OF  
HYPERTENSION AND CONGESTIVE HEART FAILURE

BACKGROUND OF THE INVENTION

5       The present invention provides a new use of known compounds. More particularly, the present invention provides for the use of 4-hydrazono-1,4-dihydro-pyridine and 4-hydrazino-pyridine derivatives for the treatment of hypertension and congestive heart failure.

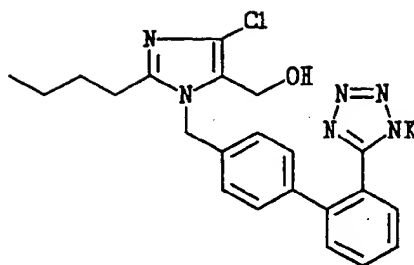
      Angiotensin II, the primary biologically active octapeptide of the renin-angiotensin-aldosterone (RAA) system, elicits a variety physiological effects, including arteriolar  
10   vasoconstriction, aldosterone biosynthesis and secretion, catecholamine release, stimulation of drinking behavior, glycogenolysis and alteration of renal function through activation of the appropriate receptor in the vasculature, adrenal cortex, adrenal medulla, brain, liver and kidney, respectively (A. T. Chiu et al., Biochem. Biophys. Res. Commun., 165, 196, 1989). During the past decade, a breakthrough in hypertension treatment has been achieved by the discovery of the  
15   angiotensin converting enzyme (ACE) inhibitors, such as captopril or enalapril, or the renin inhibitors.

      Although understanding of the causal role of the RAA system in the mosaic of essential hypertension is still incomplete, the RAA system, which is a closed-loop, negative-feedback system reacting to a reduction in renal perfusion or excessive loss of sodium, seems to be  
20   critically involved in the development and maintenance of hypertension as well as in congestive heart failure. The evidence supporting this involvement of RAA system in essential hypertension has been collected through therapeutic research using the ACE inhibitors (Tips, July 1989, Vol. 10, p. 273).

      However, the ACE inhibitors exhibit a non-specific contribution to the hydrolysis of the  
25   other substrates outside the RAA system, such as bradykinin, enkephalins, substance P, etc. Possibly due to the bradykinin potentiation, such adverse reaction as dry cough was associated with ACE inhibitors. Not only ACE but also renin was shown to have other substrates outside the RAA system. In this context, angiotensin II antagonists are considered to be the most promising approach to intervening in the RAA system.

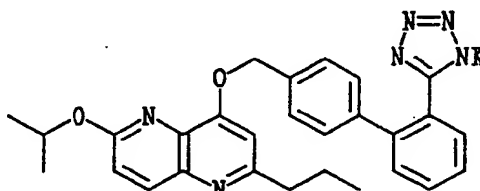
30       The putative peptidic angiotensin II antagonist Saralasin has been available for over 30 years. However, its therapeutic use has been severely limited by its partial agonistic action, short plasma half-life and lack of oral activity. Since the discovery of a "non-peptide" angiotensin II antagonist by Takeda (Japan Kokai Patent 1797-148,788, 1981-71,073 1982-98,270, 1983-157,768), extensive efforts have been made to modify or optimize this prototype  
35   lead, especially by DuPont. As a result of such efforts, orally active, competitive angiotensin II antagonist DuP 753 was discovered. The structure of this compound is set forth below.

-2-



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The head part imidazole ring of DuP 753 was found to be replaceable by benzimidazole (EP-392,317, EP-399,732, EP-400,835) or imidazopyridine ring (EP-399,731, EP-400,974, EP-415,866). Recently, pyridine or quinoline derivatives were also discovered by ICI (D-8731; EP-412,848, EP-456,442, WO-91/7404, EP-453,210) and by Meiji Seika (WO-91/19697).



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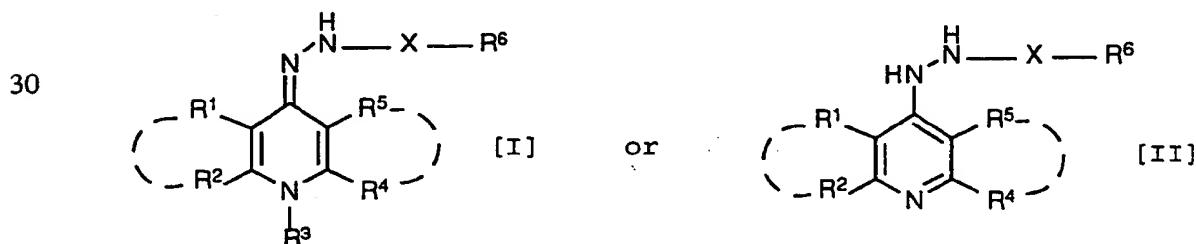
Surprisingly, the present invention provides certain 4-hydrazono-1,4-dihydro-pyridine derivatives, previously known as dyes and contract control agents, which possess angiotensin II antagonistic activity and are thus useful to treat hypertension.

#### INFORMATION DISCLOSURE

4-Hydrazono-1,4-dihydro-pyridines are well known as dyes and contrast control agents (see, e.g., U.S. Patents 4,152,152 and 3,622,327 and EPA 247845). These compounds have not been reported as useful for the treatment of hypertension or congestive heart failure.

#### SUMMARY OF THE INVENTION

The present invention provides a method for treating or preventing diseases caused by the improper functioning of the renin-angiotensin-aldosterone system comprising the systemic administration of an amount effective to inhibit the angiotensin II receptor of a compound of the formula [I] or [II], or a pharmacologically acceptable salt or ester thereof:



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wherein each occurrence of  $R^1$ ,  $R^2$ ,  $R^4$  and  $R^5$  is the same or different and is

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- (a) hydrogen,
- (b)  $C_1$ - $C_{20}$  alkyl,

- (c) C<sub>2</sub>-C<sub>20</sub> alkenyl,  
 (d) -(CH<sub>2</sub>)<sub>n</sub>-OR<sup>7</sup>,  
 (e) -(CH<sub>2</sub>)<sub>n</sub>-CONR<sup>7</sup>R<sup>8</sup>,  
 (f) aryl, or  
 5 (g) arylalkyl, or wherein  
 (h) R<sup>1</sup> and R<sup>2</sup>, or R<sup>4</sup> and R<sup>5</sup> taken together form a five or six-membered aromatic or non-aromatic ring having 0 to 2 ring members selected from sulfur or nitrogen, said ring optionally substituted by
- (i) F,  
 10 (ii) Cl,  
 (iii) Br,  
 (iv) I,  
 (v) C<sub>1</sub>-C<sub>20</sub> alkyl,  
 (vi) C<sub>2</sub>-C<sub>20</sub> alkenyl,  
 15 (vii) -(CH<sub>2</sub>)<sub>n</sub>-OR<sup>7</sup>,  
 (viii) -(CH<sub>2</sub>)<sub>n</sub>-CO<sub>2</sub>R<sup>7</sup>,  
 (ix) -(CH<sub>2</sub>)<sub>n</sub>-CONR<sup>7</sup>R<sup>8</sup>,  
 (x) -(CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>R<sup>8</sup>,  
 (xi) SO<sub>3</sub>R<sup>7</sup>, or  
 20 (xii) SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>;

wherein each occurrence of R<sup>7</sup> and R<sup>8</sup> is the same or different and is

- (a) hydrogen,  
 (b) C<sub>1</sub>-C<sub>8</sub> alkyl,  
 (c) C<sub>2</sub>-C<sub>8</sub> alkenyl,  
 25 (d) aryl, or  
 (e) arylalkyl, or  
 (f) wherein R<sup>7</sup> and R<sup>8</sup> taken together form a five or six-membered ring;

wherein R<sup>3</sup> is

- (a) hydrogen,  
 30 (b) C<sub>1</sub>-C<sub>20</sub> alkyl,  
 (c) -(CH<sub>2</sub>)<sub>n+1</sub>-CO<sub>2</sub>R<sup>7</sup>,  
 (d) -(CH<sub>2</sub>)<sub>n+1</sub>-CONR<sup>7</sup>R<sup>8</sup>,  
 (e) aryl, or  
 (f) arylalkyl;

35 wherein R<sup>6</sup> is

- (a) C<sub>1</sub>-C<sub>20</sub> alkyl,

- (b) aryl, or
- (c) biphenyl, or
- (d) arylalkyl;

wherein X is

- 5 (a) a bond,
- (b)  $\text{CH}_2$ -,
- (c)  $-\text{CO}-$
- (d)  $-\text{SO}_2$ - or,
- (e)  $-\text{SO}-$ ;

10 wherein n is an integer from 0 to 3.

Preferred compounds include:

- 1) 4-[(2-Ethyl-1-methyl-4(1H)-quinolinyldiene)hydrazino]benzoic acid
- 2) 4'-[(2-Ethyl-1-methyl-4(1H)-quinolinyldiene)hydrazino]-[1,1'-biphenyl]-2-carboxylic acid
- 3) 4'-[[[(1-Methyl-2-propyl-4(1H)-quinolinyldiene)hydrazino)methyl]-[1,1'-biphenyl]-2-
- 15 carboxylic acid
- 4) 4-[[[(2-Butyl-1-methyl-4(1H)-quinolinyldiene)hydrazino)sulfonyl]benzoic acid
- 5) 4'-[[[(2-Ethyl-1-methyl-4(1H)-quinolinyldiene)hydrazino)sulfonyl]-[1,1'-biphenyl]-2-
- carboxylic acid
- 6) Benzen-1,4-dicarboxylic acid, 4-(1-methyl-2-propyl-4(1H)-quinolinyldiene)hydrazide
- 20 7) [1,1'-Biphenyl]-2,4'-dicarboxylic acid, 4'-[1,2-dimethyl-4(1H)-quinolinyldiene)hydrazide
- 8) 2-Ethyl-1-methyl-4(1H)-quinolinone, [2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]hydrazono
- 9) 1-Methyl-2-propyl-4(1H)-quinolinone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
- yl]methyl]hydrazono
- 10) 2-Ethyl-1-methyl-4(1H)-quinolinone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
- 25 yl]sulfonyl]hydrazide
- 11) 4-[1,2,6-Trimethyl-4-(1H)-pyridinyldiene)hydrazino]benzoic acid
- 12) 4-[1-Benzyl-2,6-dimethyl-4(1H)-pyridinyldiene)hydrazino]benzoic acid
- 13) 4-[(2,6-Dimethyl-1-phenyl-4(1H)-pyridinyldiene)hydrazino]benzoic acid
- 14) 3-[[[(1,2,6-Trimethyl-4(1H)-pyridinyldiene)hydrazino)sulfonyl]benzoic acid
- 30 15) 4'-[[[(1,2,6-Trimethyl-4(1H)-pyridinyldiene)hydrazino)sulfonyl]-[1,1'-biphenyl]-2-
- carboxylic acid
- 16) 4'-[[[(1-Benzyl-2,6-dimethyl-4(1H)-pyridinyldiene)hydrazino)sulfonyl]-[1,1'-biphenyl]-2-
- carboxylic acid
- 17) 4-[[[(4-Carboxyphenyl)sulfonyl]hydrazono]-1,4-dihydro-1,2,6-trimethyl-pyridine-3-
- 35 carboxylic acid
- 18) 4-[[[(4-Carboxyphenyl)sulfonyl]hydrazono]-1,4-dihydro-1,2,6-trimethyl-3-pyridineacetic

- acid
- 19) [1,1'-Biphenyl]-2,4'-dicarboxylic acid, 4'-(2,6-diethyl-1-methyl-4(1H)-pyridinylidene)hydrazide
  - 20) 4'-[[2,6-diethyl-1-methyl-4(1H)-pyridinylidene]hydrazino]methyl-[1,1'-biphenyl]-2-carboxylic acid
  - 21) 1,2,6-Trimethyl-4(1H)-pyridone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]sulfonyl]hydrazide
  - 22) 2,6-Diethyl-1-methyl-4(1H)-pyridone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]hydrazide
  - 23) 4-(hexadecyloxy)-3-[[[2-(4-methoxy-m-tolyl)-1-methyl-6-sulfo-4(1H)-quinolylidene]hydrazino]sulfonyl]-benzoic acid
  - 24) 3-[[[2-(4-ethoxy-3-methoxyphenyl)-1-methyl-6-sulfo-4(1H)-quinolylidene]hydrazino]sulfonyl]-4-(hexadecyloxy)-benzoic acid
  - 25) 1,4-dihydro-1-methyl-4-oxo-2-[p-(p-tolyloxy)phenyl]-6-quinolinesulfonic acid, (hexadecylsulfonyl)hydrazone
  - 26) 3-[[[2-(p-carboxyphenyl)-1-methyl-6-sulfo-4(1H)-quinolylidene]hydrazino]sulfonyl]-4-(hexadecyloxy)-benzoic acid
  - 27) 4-(hexadecyloxy)-3-[[[1-methyl-2-[p-(phenylsulfonyl)phenyl]-6-sulfo-4(1H)-quinolylidene]hydrazino]sulfonyl]-benzoic acid
  - 28) 4-(hexadecyloxy)-3-[[[1-methyl-2-phenyl-6-sulfo-4(1H)-quinolylidene]hydrazino]sulfonyl]-benzoic acid
  - 29) 4-(hexadecyloxy)-3-[[[1-methyl-6-sulfo-2-m-tolyl-4(1H)-quinolylidene]hydrazino]sulfonyl]-benzoic acid
  - 30) 1,4-dihydro-1-methyl-4-oxo-2-phenyl-6-quinolinesulfonic acid, [[m-(hexadecylmethylsulfamoyl)phenyl]sulfonyl]-hydrazone
  - 31) [p-[[[2-[p-(hexadecyloxy)phenyl]-1-methyl-6-sulfo-4(1H)-quinolylidene]hydrazino]sulfonyl]phenoxy]-acetic acid
  - 32) [6-acetamido-1-methyl-2-(p-sulfophenyl)-4(1H)-quinolylidene]hydrazide hexadecanesulfonic acid, sodium salt
  - 33) 2-(3,4-dimethoxyphenyl)-1,4-dihydro-1-methyl-4-oxo-6-quinolinesulfonic acid, (hexadecylsulfonyl)hydrazone
  - 34) 5-[[[2-[p-(hexadecyloxy)phenyl]-1-methyl-6-sulfo-4(1H)-quinolylidene]hydrazino]sulfonyl]-salicylic acid
  - 35) 4-[(hexadecylsulfonyl)-hydrazono]-1-methyl-2-phenyl-5-quinolinesulfonic acid
  - 36) 2-(2-fluorophenyl)-4-[(hexadecylsulfonyl)hydrazono]-1,4-dihydro-1-methyl-6-quinolinesulfonic acid

The 4-hydrazono-1,4-dihydro-pyridine/4-hydrazino-pyridine derivatives of the present invention can form a pharmacologically acceptable ester at a part of  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$  and  $R^6$  in the general formula [I]. As examples of the formed ester, there are methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, t-butoxycarbonyl, 2-hydroxyethoxycarbonyl or 3-hydroxypropoxycarbonyl, in case  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$  has carboxylic acid substituent. There are acetoxyl, n-propionyl, butyryl, valeryl or hexanoyl, in case substituent is a hydroxyl group. Examples of aryl include phenyl, biphenyl, and substituted derivatives thereof.

Further, the 4-hydrazono-1,4-dihydro-pyridine/4-hydrazino-pyridine derivatives of the present invention can form a pharmacologically acceptable alkali metal salt as a part of  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$  and  $R^6$  when substituted by  $-SO_3H$ ,  $-CO_2H$  or tetrazole. As examples of salts as a part of amine moiety within the 4-hydrazono-1,4-dihydro-pyridine/4-hydrazino-pyridine structures, there are hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate, tartrate and the like.

The compounds of the present invention are useful whenever it is medically necessary or desirable to inhibit the renin-angiotensin-aldosterone system. The angiotensin II receptor antagonist compounds of the present invention are thus administered to humans to treat or prevent a variety of cardiovascular disorders related to the improper functioning of the renin-angiotensin-aldosterone system including hypertension, congestive heart failure, renal failure, glaucoma, or hyperuricemia. Such conditions are readily apparent to an ordinarily skilled physician. Treatment or prevention of hypertension or congestive heart failure are the preferred cause of using these compounds.

By "treat" is meant the partial or total alleviation of the symptoms of the disease manifested in the patient. By "prevent" is meant the partial or total avoidance of the symptoms of the disease in a patient who is otherwise believed by the physician to be susceptible to such disease or condition.

The 4-Hydrazono-1,4-dihydro-pyridine and/or 4-hydrazino-pyridine derivatives or pharmacologically acceptable esters or salts thereof are administered orally, parenterally by insufflation, rectally, locally. Parenteral administration includes subcutaneous, intravenous, intramuscular, intranasal administration or injection. Dose to be administered an adult is in a range of 1 to 500 mg/day. The exact dose can be selected from the above range, taking into account the age of patient, weight, condition to be treated and route of administration into consideration. The frequency of administration is usually one to four times a day.

The 4-hydrazono-1,4-dihydro-pyridine/4-hydrazino-pyridine derivatives or pharmacologically acceptable ester or salts thereof can be formulated, by a conventional method, into a dosage unit forms such as tablets, capsules, pills, powder, granules, powder packet,

cachets, sterile parenteral solution or suspensions, eyedrops, solutions or suspensions, elixirs, suppositories, aerosols and emulsions which contains them in a predetermined amount.

For oral administration, solid or fluid unit dosage form can be prepared. For preparing solid composition, the active compound is mixed with an excipient or a carrier such as magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulphate, starch, lactose, acacia, ethyl cellulose and the like. A capsule agent is prepared by mixing the compound of the present invention with an inert pharmaceutical excipient, filling the mixture into a hard gelatin capsule having suitable size. A soft gelatin capsule is prepared by machine capsulation of slurry composed of the compound, suitable vegetable oil, light petrolatum or other inert oil.

For preparing a fluid composition, the compound of the present invention is dissolved in an aqueous vehicle together with sugar, aromatic flavor and preservative to obtain a syrup. Elixirs are prepared using an alcoholic vehicle such as ethanol, a sweetener such as sugar and saccharin as well as a flavor. Suspensions are prepared using a suspending agent such as acacia, tragacanth or methyl cellulose and an aqueous vehicle.

For parenteral administration, a fluid unit dosage form is prepared using the compound of the present invention and a sterile vehicle. Depending upon a vehicle such as water, Ringer's solution, isotonic sodium chloride solution and the concentration to be used, the compound is suspended or dissolved in the vehicle. For preparing solutions, the compound is dissolved in water for injection, and this is sterile filtered, filled into a vial for an ampoule, and sealed. Advantageously, an adjuvant such as local anesthetic, preservative and buffer is dissolved in vehicle. Alternatively, a lyophilized powder having good shelf stability can be prepared. In the case of this formulation, the powder is reconstituted upon use. Parenteral suspensions can be similarly prepared using the compound of the present invention. In the case of this formulation, the compound of the present invention can be sterilized by exposure to ethylene oxide before suspended in a sterile vehicle. Advantageously, a surfactant or a wetting agent is added to facilitate dispersion of the compound.

Alternatively, the compound of the present invention can be formulated into a local dosage form in combination with a suitable carrier for local administration. Examples of a carrier to be used are cream, ointment, lotion, paste, jelly, spray, aerosol and the like.

Further, when other form cannot be administered, suppositories can be prepared. Examples of a base are cacao butter, polyethylene glycol, polyethylene sorbitan monostearate and the like.

4-Hydrazono-1,4-dihydro-pyridine/4-hydrazino-pyridine derivatives represented by the general formula [I] are well known, readily available compounds and can be purchased from standard chemical manufacturers such as Eastman Kodak, and/or can be prepared by known

means, see, e.g., U.S. Patents 4,152,152 and 3,622,327 and EPA 247845. They can be prepared, for example, according to the following scheme. (See Chart A).

General formula [I] can be prepared according to the procedures reported by H. Vorbrüggen, *Synthesis* 301 (1973) by reacting the appropriate 4-pyridones (1) or 4-hydroxypyridines (3) with optionally substituted hydrazines. Alternatively, as stepwise methods, the compounds [I] can be obtained by alkylation, acylation or sulfonylation of the corresponding hydrazones (2) or hydrazines which are formed from the reaction of (1) or (3) with hydrazine.

4-Hydroxypyridines can be converted to 4-halogeno-pyridines by reacting with phosphorus tri-or penta-halides, phosphoryl chloride or thionylchloride [K. Heyns and G. Vogelsang, *Chem. Ber.* 87:13 (1954)] which can be subsequently converted to the claimed compounds, according to the procedures reported by D. S. Tarbell, et al., *J. Am. Chem. Soc.* 70:1381 (1948).

4-Aminoquinoline derivatives are prepared from the corresponding 4-quinolone through chlorination by phosphorus oxychloride followed by amination with ammonia in thermal conditions. 4-Hydrazono-1,4-dihydro-pyridine and/or 4-hydrazino-pyridine derivatives were also easily prepared by similar reactions.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof. The Pharmacological evaluation of the compounds of the present invention is described hereinafter.

##### TEST 1      In vitro Ang II receptor binding assay

Rat liver homogenates are prepared as follows: Adult rats (10-25) are decapitated and the livers excised free of connective tissue. They are held in a container of cold 0.05 M TRIS buffer (pH8.). Four to six livers are placed in a waring blender, covered with fresh cold Tris buffer, and homogenized. This material is then further homogenized with the glass homogenizer and filtered through a four layer thickness of gauze into 250 mL centrifuge bottles on ice. This procedure is repeated until four bottles have been filled. The material is centrifuged in a swinging bucket rotor for 30 min at 1500 g(max), 4°C. The supernatant is carefully decanted and the pellet is resuspended in 0.05M TRIS (pH8.0) and resuspended with the glass homogenizer to reduce large clumps. Sucrose solution (69-70%) is added to the liver homogenate until the final concentration is ca. 44% (w/w). This solution is dispensed into Beckman ultracentrifuge tubes, about 28-30 mL per tube. These solutions are carefully overlaid with 10 mL of a 42.3% sucrose solution (w/w). This material is centrifuged for 120 min at 25,000 rpm in an SW28 rotor. The material that has floated to the surface is collected using a spatula and resuspended in about 8 mL of TRIS buffer. This material is then placed in a 50 mL syringe, passed through a 20G needle and pipetted in 0.1, 0.5, and 1.0 aliquots into

ependorf tubes. The protein concentration is also ascertained. These tubes are frozen in dry ice-acetone and stored at -80 C.

25 $\mu$ L of the 0.05 M TRIS buffer is added to the wells in the counter designated for Total Binding (TB). 25  $\mu$ L of 10  $\mu$ M ang II are added to the control wells designated for Non-Specific Binding (NSB) usually and 25  $\mu$ L of the 5 nM angII is added to wells as experimental controls. The rat liver homogenate is removed from the -80°C freezer and thaw on ice. The homogenate is diluted with angII assay buffer to a protein concentration of ca. 0.1 mg/mL. 100  $\mu$ L of this diluted receptor source is added to all wells containing 25  $\mu$ L of dispensed samples to test. (After addition of ligand, the protein concentration is about 45 ng/mL). 11 mL of diluted receptor is prepared per assay plate.

Radioligand is prepared using  $^{125}$ I-angII (50  $\mu$ Ci/mL; 2,000 mCi/mmol) and unlabeled 100 nM angII. Per assay plate, 172  $\mu$ L of the first and 26  $\mu$ L of the second are diluted with 12.8 mL of angII assay buffer. 125  $\mu$ L of this material is added per well in the assay plate. (This will give an angII concentration in the assay of ca. 0.25 nM, lower than the Kd for this compound, but sufficient to provide a good indication of antagonism.) The total added cpm generally runs around 100,000 to 130,000.

The sequence of addition for the materials is sample to be tested, rat liver homogenate and finally the ligand. By adding in this sequence, sufficient initial mixing occurs that stirring or shaking is not necessary. The plates are then incubated for 2 hours at 37° C in a humidified incubator. After this time, samples are collected on Printed Filter Mat B using the Skatron MicroCell Harvester. Care should be taken that the filter mats and assay plates are oriented correctly. The filter mats are dried at room temperature in a circulated air drying oven. The mats are bagged, the long side sealed, and one end cut. To this cut end one adds ca. 20 mL of scintillation fluid. Scintillant is distributed over the entire filter using a roller, the end resealed and placed into holders for counting on the LKB Beta-Plate using program 7. Again, care should be taken as to the correct orientation of the filter mat. The data are captured both on a 3.5" floppy disc and on paper.

**TEST 2** In vitro antagonism to Ang II constriction in an isolated rabbit thoracic aorta.

A rectangular strip-like sample of thoracic aorta isolated from an anesthetized rabbit was prepared, and this was suspended at 2.0 gr of loaded tension in Magnus tube filled with Krebs-Henseleitoid nutrition solution which was well aerated with 95% O<sub>2</sub> - 5% CO<sub>2</sub>, and the constriction tension was measured using an isometric transducer. After the tension of the sample at rest became stable, accumulative administration of Ang II was carried out to obtain a concentration-action curve. Thereafter, the sample was washed with the same nutrition solution, and then 10<sup>-5</sup> - 10<sup>-6</sup> M test compound was treated for 20 min. to obtain again a concentration-action curve of Ang II. The results were obtained as follows: generated maximum tension at

the first accumulative administration of Ang II was regarded as 100%, and the 50% effective concentration ( $ED_{50}$ ) was obtained in the presence or absence of the test compound, and  $pA_2$  value was calculated according to the following equations:

$$pA_2 = -\log K_B \quad K_B = C / [(A'/A) - 1]$$

5

C: concentration of the test compound (M)

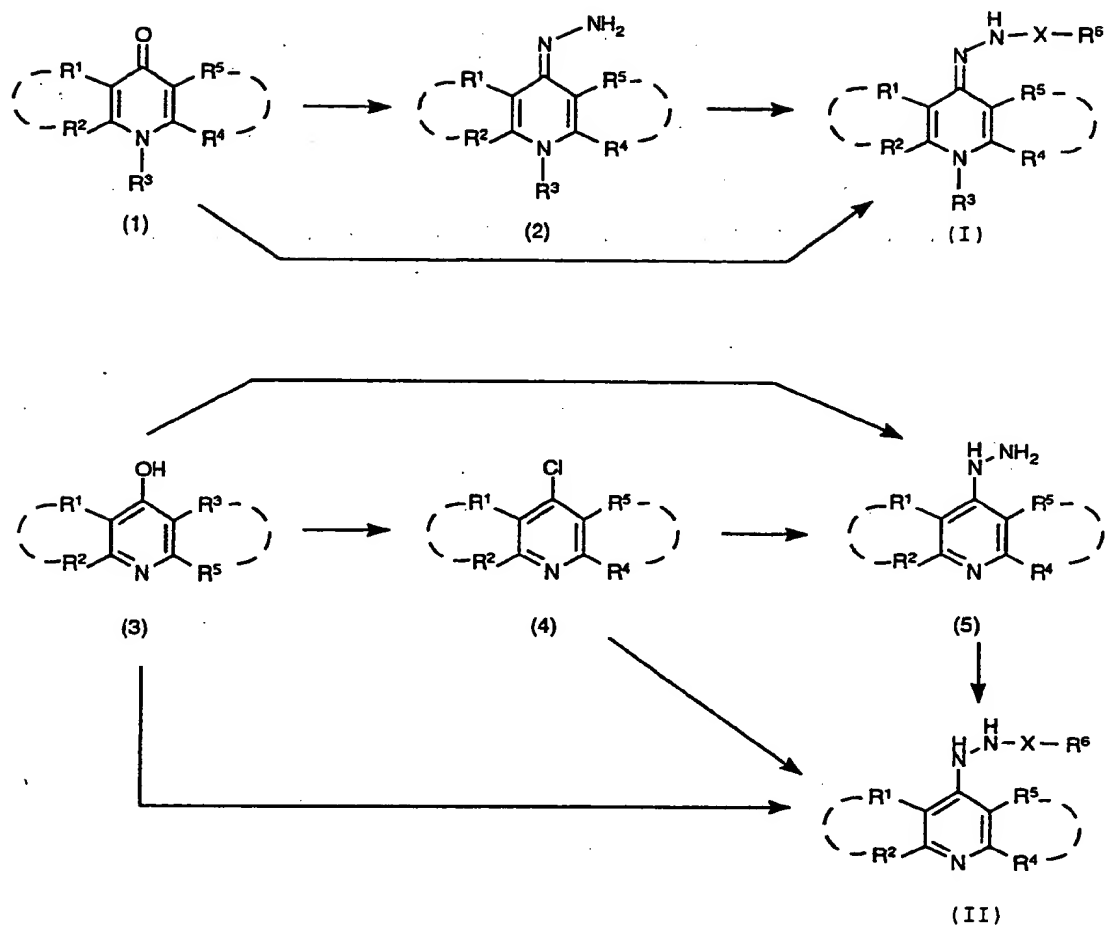
A':  $ED_{50}$  in the presence of test compound (M)

A:  $ED_{50}$  in the absence of the test compound (M)

In above tests, compounds of the present invention showed Ang II antagonistic activity.

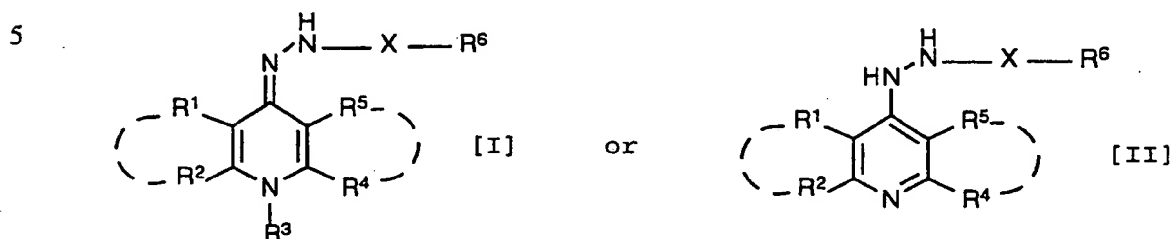
10 All of the compounds 1-36 listed herein showed activity in one or both of these tests. For example, the compound No. 23 and 27 showed 90 and 82% inhibition in Test 1, respectively. And the compounds No. 23 and 27 showed  $pA_2$  value of 5.51 and 5.32 in test 2, respectively.

## CHART A



## CLAIMS

1. Use of a 4-hydrazono-1,4-dihydro-pyridine and/or 4-hydrazino-pyridine derivative of the formula [I] or [II]



or a pharmacologically acceptable salt or ester thereof,

wherein each occurrence of R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>5</sup> is the same or different and is

- (a) hydrogen,
- (b) C<sub>1</sub>-C<sub>20</sub> alkyl,
- (c) C<sub>2</sub>-C<sub>20</sub> alkenyl,
- (d) -(CH<sub>2</sub>)<sub>n</sub>-OR<sup>7</sup>,
- (e) -(CH<sub>2</sub>)<sub>n</sub>-CONR<sup>7</sup>R<sup>8</sup>,
- (f) aryl, or
- (g) arylalkyl, or wherein
- (h) R<sup>1</sup> and R<sup>2</sup>, or R<sup>4</sup> and R<sup>5</sup> taken together form a five or six-membered aromatic or non-aromatic ring having 0 to 2 ring members selected from sulfur or nitrogen, said ring optionally substituted by

- (i) F,
- (ii) Cl,
- (iii) Br,
- (iv) I,
- (v) C<sub>1</sub>-C<sub>20</sub> alkyl,
- (vi) C<sub>2</sub>-C<sub>20</sub> alkenyl,
- (vii) -(CH<sub>2</sub>)<sub>n</sub>-OR<sup>7</sup>,
- (viii) -(CH<sub>2</sub>)<sub>n</sub>-CO<sup>2</sup>R<sup>7</sup>,
- (ix) -(CH<sub>2</sub>)<sub>n</sub>-CONR<sup>7</sup>R<sup>8</sup>,
- (x) -(CH<sub>2</sub>)<sub>n</sub>-NR<sup>7</sup>R<sup>8</sup>,
- (xi) SO<sub>3</sub>R<sup>7</sup>, or
- (xii) SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>;

wherein each occurrence of R<sup>7</sup> and R<sup>8</sup> is the same or different and is

- (a) hydrogen,

- (b) C<sub>1</sub>-C<sub>8</sub> alkyl,  
 (c) C<sub>2</sub>-C<sub>8</sub> alkenyl,  
 (d) aryl, or  
 (e) arylalkyl, or  
 5 (f) wherein R<sup>7</sup> and R<sup>8</sup> taken together form a five or six-membered ring;

wherein R<sup>3</sup> is

- (a) hydrogen,  
 (b) C<sub>1</sub>-C<sub>20</sub> alkyl,  
 (c) -(CH<sub>2</sub>)<sub>n+1</sub>-CO<sup>2</sup>R<sup>7</sup>,  
 10 (d) -(CH<sub>2</sub>)<sub>n+1</sub>-CONR<sup>7</sup>R<sup>8</sup>,  
 (e) aryl, or  
 (f) arylalkyl;

wherein R<sup>6</sup> is

- (a) C<sub>1</sub>-C<sub>20</sub> alkyl,  
 15 (b) aryl, or  
 (c) biphenyl, or  
 (d) arylalkyl;

wherein X is

- (a) a bond,  
 20 (b) CH<sub>2</sub>-,  
 (c) -CO-  
 (d) -SO<sub>2</sub>- or,  
 (e) -SO-;

wherein n is an integer from 0 to 3 to prepare a medicament to treat or prevent diseases  
 25 caused by the improper functioning of the renin-angiotensin-aldosterone system.

2. A use of claim 1, wherein the disease is hypertension.
3. A use of claim 1, wherein the disease is congestive heart failure.
- 30 4. A use of claim 1, wherein the compound is selected from the group consisting of:
- 1) 4-[(2-Ethyl-1-methyl-4(1H)-quinolinyldene)hydrazino]benzoic acid
  - 2) 4'-[(2-Ethyl-1-methyl-4(1H)-quinolinyldene)hydrazino]-[1,1'-biphenyl]-2-carboxylic acid
  - 35 3) 4'-[[1-Methyl-2-propyl-4(1H)-quinolinyldene)hydrazino]methyl]-[1,1'-biphenyl]-2-carboxylic acid

- 4) 4-[[2-Butyl-1-methyl-4(1H)-quinolinyldene]hydrazino]sulfonyl]benzoic acid
- 5) 4'-[[2-Ethyl-1-methyl-4(1H)-quinolinyldene]hydrazino]sulfonyl]-[1,1'-biphenyl]-2-carboxylic acid
- 6) Benzen-1,4-dicarboxylic acid, 4-(1-methyl-2-propyl-4(1H)-quinolinyldene)hydrazide
- 7) [1,1'-Biphenyl]-2,4'-dicarboxylic acid, 4'-[1,2-dimethyl-4(1H)-quinolinyldene]hydrazide
- 8) 2-Ethyl-1-methyl-4(1H)-quinolinone, [2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]hydrazone
- 9) 1-Methyl-2-propyl-4(1H)-quinolinone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]hydrazone
- 10) 2-Ethyl-1-methyl-4(1H)-quinolinone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]sulfonyl]hydrazide
- 11) 4-[1,2,6-Trimethyl-4(1H)-pyridinyldene]hydrazino]benzoic acid
- 12) 4-[1-Benzyl-2,6-dimethyl-4(1H)-pyridinyldene]hydrazino]benzoic acid
- 13) 4-[(2,6-Dimethyl-1-phenyl-4(1H)-pyridinyldene)hydrazino]benzoic acid
- 14) 3-[[[(1,2,6-Trimethyl-4(1H)-pyridinyldene)hydrazino]sulfonyl]benzoic acid
- 15) 4'-[[[(1,2,6-Trimethyl-4(1H)-pyridinyldene)hydrazino]sulfonyl]-[1,1'-biphenyl]-2-carboxylic acid
- 16) 4'-[[[(1-Benzyl-2,6-dimethyl-4(1H)-pyridinyldene)hydrazino]sulfonyl]-[1,1'-biphenyl]-2-carboxylic acid
- 17) 4-[[[(4-Carboxyphenyl)sulfonyl]hydrazono]-1,4-dihydro-1,2,6-trimethyl-pyridine-3-carboxylic acid
- 18) 4-[[[(4-Carboxyphenyl)sulfonyl]hydrazono]-1,4-dihydro-1,2,6-trimethyl-3-pyridineacetic acid
- 19) [1,1'-Biphenyl]-2,4'-dicarboxylic acid, 4'-(2,6-diethyl-1-methyl-4(1H)-pyridinyldene)hydrazide
- 20) 4'-[[[(2,6-diethyl-1-methyl-4(1H)-pyridinyldene)hydrazino]methyl]-[1,1'-biphenyl]-2-carboxylic acid
- 21) 1,2,6-Trimethyl-4(1H)-pyridone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]sulfonyl]hydrazide
- 22) 2,6-Diethyl-1-methyl-4(1H)-pyridone, [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]hydrazide
- 23) 4-(hexadecyloxy)-3-[[[2-(4-methoxy-m-tolyl)-1-methyl-6-sulfo-4(1H)-quinolinyldene]hydrazino]sulfonyl]-benzoic acid
- 24) 3-[[[2-(4-ethoxy-3-methoxyphenyl)-1-methyl-6-sulfo-4(1H)-

- quinolinylidene]hydrazino]-sulfonyl]-4-(hexadecyloxy)-benzoic acid
- 25) 1,4-dihydro-1-methyl-4-oxo-2-[p-(p-tolyloxy)phenyl]-6-quinolinesulfonic acid,  
(hexadecylsulfonyl)hydrazone
- 26) 3-[[[2-(p-carboxyphenyl)-1-methyl-6-sulfo-4(1H)-  
5 quinolylidene]hydrazino]sulfonyl]-4-(hexadecyloxy)-benzoic acid
- 27) 4-(hexadecyloxy)-3-[[[1-methyl-2-[p-(phenylsulfonyl)phenyl]-6-sulfo-4(1H)-  
quinolinylidene]hydrazino]sulfonyl]-benzoic acid
- 28) 4-(hexadecyloxy)-3-[[[1-methyl-2-phenyl-6-sulfo-4(1H)-  
quinolylidene]hydrazino]sulfonyl]-benzoic acid
- 10 29) 4-(hexadecyloxy)-3-[[[1-methyl-6-sulfo-2-m-tolyl-4(1H)-  
quinolylidene]hydrazineo]sulfonyl]-benzoic acid
- 30) 1,4-dihydro-1-methyl-4-oxo-2-phenyl-6-quinolinesulfonic acid, [[m-  
(hexadecylmethylsulfamoyl)phenyl]sulfonyl]-hydrazone
- 31) [p-[[[2-[p-(hexadecyloxy)phenyl]-1-methyl-6-sulfo-4(1H)-  
15 quinolinylidene]hydrazino]sulfonyl]phenoxy]-acetic acid
- 32) [6-acetamido-1-methyl-2-(p-sulfophenyl)-4(1H)-quinolylidene]hydrazide  
hexadecanesulfonic acid, sodium salt
- 33) 2-(3,4-dimethoxyphenyl)-1,4-dihydro-1-methyl-4-oxo-6-quinolinesulfonic acid,  
(hexadecylsulfonyl)hydrazone
- 20 34) 5-[[[2-[p-(hexadecyloxy)phenyl]-1-methyl-6-sulfo-4(1H)-  
quinolylidene]hydrazino]sulfonyl]-salicylic acid
- 35) 4-[(hexadecylsulfonyl)-hydrazono]-1-methyl-2-phenyl-5-quinolinesulfonic acid
- 36) 2-(2-fluorophenyl)-4-[(hexadecylsulfonyl)hydrazono]-1,4-dihydro-1-methyl-6-  
quinolinesulfonic acid
- 25

# INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/US 93/08156

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 5 A61K31/44 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J.MED.CHEM. vol. 14, no. 11, 1971 pages 1066 - 1066 G.C.WRIGHT ET AL. 'SYNTHESIS AND HYPOTENSIVE PROPERTIES OF NEW 4-AMINOQUINOLINES' table I, compound 41	1-4
A	US,A,4 980 379 (BELARDINELLI ET AL.) 25 December 1990 see column 6, line 46	1-4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

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Date of the actual completion of the international search

1 December 1993

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17. 12. 93

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